PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Weadock et al.

Examiner: Paul B. Prebilic

Application No.: 09/391,762

Group Art: 3738

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Date: April 11, 2005

For: TUBULAR EXPANDED POLYTETRAFLUOROETHYLENE IMPLANTABLE PROSTHESIS

I hereby certify this correspondence is being deposited with United States Postal Service as first class mail, postpaid in an envelope, addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Date: April 11, 2005
Signature /Barbara Thomas/

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GARY LOOMIS, Ph.D.
PURSUANT TO 37 C.F.R. §1.132

Sir:

I, Gary Loomis, Ph.D., do hereby make the following declaration:

1. A copy of my curriculum vitae is attached as Exhibit A. As noted therein, I received a M.A. in Chemistry in 1973 from The Johns Hopkins University, in Baltimore, Maryland. I also received a Ph.D. in Organic Chemistry (with a minor in biochemistry) from The Johns Hopkins University in 1975. I subsequently conducted post doctoral studies as a National Institutes of

Health research fellow at the Imperial College of Science and Technology, in London, England, from 1975-1977, and at L'Ècole Normale Supérieure, in Paris, France, from 1977-1978.

2. I have worked in the field of polymer chemistry continuously since 1979.

3. I have over twenty years of experience in academic and industrial settings. I was a Senior Research Scientist at E.I. DuPont Co. for twelve years, where my focus included development of bioresorbable compositions for medical device applications and resulted in the formation of the Medisorb® family of polymers. I subsequently worked as a Senior Research Manager for Warner Lambert Co. in their biodegradable starch products division. Additionally, I was Chief Scientific Officer for Provasis Therapeutics, Inc., where I developed polymers for *in vivo* treatment of neurovascular disorders. I also have been a consultant for numerous companies since 1993. My experience with biodegradable materials is in the field of endovascular prostheses and other medical devices and includes work with proteins, polysaccharides, and polylactides for endovascular, drug delivery, orthopedic and coronary imaging applications, to name a few.

4. During the course of my employment, and as noted in Exhibit A, I was named as an inventor on various patents that relate to biodegradable materials and/or to endovascular prostheses and other medical devices.

5. I have reviewed a copy of U.S. Application No. 09/391,762.

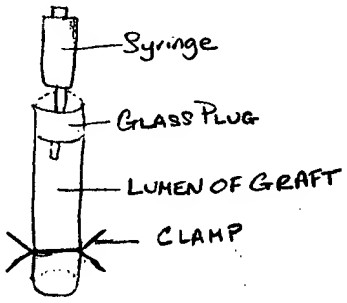
6. I have thoroughly read and understand the Office Action dated November 10, 2004 (which was issued in connection with U.S. Application No. 09/391,762) and the following references which were cited therein: Kaehler et al., *Journal of Vascular Surgery*, 9(4) (April 1989) (hereinafter "Kaehler"); U.S. Patent No. 5,197,977 (hereinafter "Hoffman '977"); Tran and Walt, *Journal of Colloid and Interface Science*, 132(2) (October 15, 1989) (hereinafter

"Tran"); and U.S. Patent No. 5,037,377 (hereinafter "Alonso"). I also have reviewed the specification and claims of U.S. Patent Application No. 09/391,762.

7. It is my belief, based on my review of the Kaehler reference, that the procedure described in the first full paragraph at the right-hand column on page 536 is not intended to fill, or even substantially fill, the pores of the PTFE graft described therein with a solid material or precipitate of any kind. Rather, the procedure set forth in that paragraph is a procedure for precoating the inner surface of a graft with a mixture of collagen types I and III. The procedure involves adjusting the pH of a solution containing a commercially available mixture of collagen types I and III to a pH of 7.2 and then injecting the resultant mixture into the lumen of a PTFE graft. After that procedure is repeated three times, excess collagen is removed, the graft is heated at 37° C to form a coating on the inner surface of the graft, and the graft is dried. To the best of my understanding, that entire procedure is then repeated twice to make the coating thicker, and the resulting graft is then dried. In my opinion, only an incidental amount of collagen, if any, would end up in the pores of the PTFE graft as a result of this procedure. Accordingly, I would not conclude that the pores are filled or substantially filled with collagen or any other solid material of natural origin. Moreover, there is no suggestion in Kaehler of an implantable member where the pores of an expanded polytetrafluoroethylene substrate are filled or substantially filled with a solid precipitate of a material of natural origin formed *in situ* from a solution that is pH-adjusted within the pores of the graft. Indeed, Kaehler's very protocol requires that the pH of the solution be changed prior to application to a PTFE graft.

8. I note that Kaehler states on page 536 (right column, first full paragraph) that a collagen "solution" having a pH of 7.2 was "forced through the graft interstices." However, based on my experience with collagen, Kaehler could not possibly have been using a true solution at that pH. In particular, at least some collagen precipitate would already have been present in the medium at a pH of 7.2. Accordingly, Kaehler must have been using a suspension or slurry of collagen.

9. Moreover, in view of the experimental design set forth in the third full paragraph on page 536 (left-hand column), and Kaehler's overall objective of evaluating precoating substrates for the endothelial cell lining of PTFE grafts, I am of the opinion that Kaehler was not literally forcing any collagen through graft interstices. Rather, it is my understanding that Kaehler was merely injecting a suspension or slurry of collagen through a graft that was fitted at one end with a glass plug and syringe and clamped at the other end. Such an apparatus may have appeared as follows:



10. Upon the initial injection of the collagen suspension or slurry into the graft, air would have been displaced through the pores of the graft. However, once the graft was subsequently treated in accordance with the experimental procedure set forth in the first full paragraph at the right-hand column of page 536 to form a coating on the inner surface of the graft, the coating would have prevented air from being displaced through the pores. As a result, air would have become trapped in the clamped graft, making it increasingly difficult to inject the contents of the syringe into the lumen of the graft.

11. Accordingly, I do not interpret Kaehler's statement at page 536 that "[o]n the third occasion it was almost impossible to force the solution through the graft" as necessarily indicating that a precipitate of collagen was present in the pores of the graft. Rather, I interpret that statement as meaning that it became almost impossible to inject the contents of the syringe into the lumen of the clamped graft. Thus, it is my opinion that Kaehler most likely was merely forcing the contents of the syringe into the lumen of the clamped graft and not into the graft interstices.

12. If a collagen suspension or slurry were truly forced through the interstices of the graft, I would expect that a coating would appear on both the inner and outer surfaces of the graft. However, there is no indication that any collagen is present on the outer surface of the graft.

13. While "interstices filling matrices" are mentioned at page 537, left column, fourth full paragraph, no experimental data is presented to suggest that any precipitate is present in the pores of the graft, much less that the pores are substantially or completely filled with a solid material. In this regard, nothing in the SEM results discussed in Kaehler leads me to believe that Kaehler was concerned with impregnating the pores of the PTFE graft with collagen or any other material. In fact, the SEM results could be interpreted as consistent with Kaehler's express representation in the abstract that the PTFE graft is merely coated. In particular, Kaehler on page 537 indicates that "[u]nder low magnification the SEM appearance of the surfaces was generally smooth, only occasionally showing shallow folds parallel to the nodes of the graft material." Moreover, Kaehler also indicates on page 537 that the graft area showed "a grossly even distributed layer" and that the collagen type I/III mixture "completely covered the underlying PTFE material." These statements, to me, are consistent with my understanding that Kaehler is only coating the surfaces of the PTFE grafts. Indeed, the very purpose of taking the SEM micrografts was to evaluate the surface characteristics of the grafts after applying the collagen type I/III mixture. Accordingly, Kaehler may have been using the phrase "interstices filling matrices" in a way that is different than the way in which a polymer chemist skilled in the art of making medical devices would use that phrase.

14. As used in the art, coating a graft typically refers to covering a graft and is standard practice. There is a distinct difference between coating a PTFE graft and impregnating the pores of an ePTFE graft as taught in U.S. Application No. 09/391,762.

15. Based on my review of the Kaehler reference, the procedure described in the first full paragraph at the right-hand column of page 536 is only one-step in Kaehler's overall experimental study. In particular, after Kaehler has prepared grafts having a coating that

contains collagen types I and III (in the manner discussed at the first full paragraph at the right-hand column of page 536), Kaehler then adds various additional coatings to the grafts.

16. One such additional coating process is described in the fourth full paragraph at the right-hand column of page 536 where Kaehler discloses dissolving a very small amount of type IV collagen (i.e., 1 milligram) in HCl to form a solution containing HCl and collagen. It is my understanding that a graft that is coated with collagen types I and III is filled with the HCl solution and then rotated several times. Thereafter, the solution is allowed to run out of the graft, and the graft is rinsed. The graft is then subjected to a 60-minute HFN treatment as described in the fourth full paragraph at the left-hand column on page 536. I understand this process to result in a graft having a first underlying coating that contains collagen types I and III and a second, much thinner coating containing collagen type IV and HFN atop of the first coating.

17. Nothing in Kaehler suggests placing an acidic solution in the pores of a PTFE graft, much less adjusting the pH within the pores to obtain a precipitate of a material of natural origin. Indeed, the HCl solution discussed on page 536 would never reach the pores of the PTFE because of the underlying coating of collagen types I and III, which as described by Kaehler, "completely covered the underlying PTFE material" as "a densely woven mat." (see Kaehler, page 537, paragraph bridging the columns). Accordingly, nowhere does Kaehler suggest placing a solution of a biodegradable composition having an acidic pH in the pores of an expanded polytetrafluoroethylene graft for the purpose of forming an insoluble substrate site for cellular attachment as taught by U.S. Application No. 09/391,762.

18. Although I am not familiar with the curriculum vitae of the authors of the Kaehler reference, I note that they are physicians. I would not expect physicians to necessarily describe experimental procedures and results involving PTFE grafts in the same way that a polymer chemist who is skilled in the art of making such medical devices might. Accordingly, my opinions with regard to the Kaehler reference are based on the overall disclosure of Kaehler coupled with my own knowledge of collagen and PTFE grafts.

19. Based on my review of the Hoffman '977, Alonso, and Tran references, there is no disclosure, teaching or suggestion in any of those references to precipitate a material of natural origin out of a solution *in situ* by means of pH-adjustment of the solution within the pores of an expandable polytetrafluoroethylene substrate of an implantable member. Indeed, there is no teaching or suggestion to fill or substantially fill the pores of a graft in such a manner. Moreover, none of the references would lead me to make an implantable member having an expanded polytetrafluoroethylene substrate with pores that contain a solution of a biodegradable composition having an acidic pH, let alone such an implantable member where the biodegradable composition is capable of forming a precipitate that substantially fills the pores at selected conditions of temperature and pH to form an insoluble substrate site for cellular attachment. In fact, if I were working with PTFE grafts, I would not even consult the Hoffmann '977 and Alonso references as those references pertain to textile grafts and not PTFE grafts. Moreover, as the discussion in Tran merely pertains to making a chemically inert surface active, I also would not necessarily consult Tran.

20. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 8th day of April, 2005.

Gary Loomis, Ph.D.

Gary L. Loomis, Ph.D.
(G. L. Loomis & Associates, Inc.)
Curriculum Vitae

Summary:

Creative, individual known internationally for the development of materials for biomedical applications. Combines excellent technical, business, management and communications skills with the ability to interact with people of varied disciplines at all organizational levels. Particular expertise in applications of bioresorbable polymers for functional implantable devices, blood-contacting devices, controlled release of pharmologically active agents, and matrices for tissue engineering.

Recent projects include:

- Development of compositions and processes leading to novel liquid embolic systems trademarked Neuracryl® (through phase 1 clinical trial).
- Valuable contributions to the development of vascular grafts with bioresorbable hydrogel coatings.
- Transfer of technology involving a process for coating cardiovascular stents with a pharmacologically active polymer.
- Technical assessments of intellectual property (due diligence).
- Development of novel procedures for the stabilization, sterilization, and analysis of clinically useful reactive monomers.

Experience:

1993 to Present — G. L. Loomis & Associates Inc., Solana Beach, CA and Morristown, NJ
Founder and President

Founder and senior consultant of a firm providing technical guidance to a diverse international client base ranging from start-up enterprises to Fortune 100 corporations. In addition to personal consulting activities, direct and manage technical associates who are all recognized experts with decades of practical experience in their respective fields. Particular expertise in polymeric biomaterials, hydrogels, and resorbable materials for use in biomedical products. Services have included advising on the selection, synthesis, modification, evaluation, and processing of materials for biomedical applications; design of products and processes; intra- and inter-

company technology transfer; formulation of patent strategies; technical due diligence; and technical expert testimony relating to IP litigation.

2001 to 2003 — Provasis Therapeutics Inc., San Diego, CA
Chief Scientific Officer and Vice President, R&D

Senior management executive responsible for all technical issues relating to the development and commercialization of embolic agents (Neuracryl®) for the minimally invasive treatment of neurovascular disorders. Responsibilities included staffing and equipping of R&D department, development of strategic alliances with development partners, development of commercial processes for the manufacture and purification of requisite monomers and polymers, assembly of devices, and evaluation of competing technologies.

Functioned as the 'in-house' patent director and as such assume responsibility for all Provasis intellectual property (IP). Implemented a comprehensive new patent strategy and assisted in preparation of new applications for domestic and to supplement existing portfolio. Assist attorneys performing IP due diligence for potential investors. Managed annual R&D budget in excess of $5MM.

1991 to 1993 — Warner Lambert Co., Morris Plains, NJ
Senior Research Manager (director level) - Novon Products Division

Novon Products was an ambitious, start-up venture aimed at the development of biodegradable thermoplastics based on natural polysaccharides. Such materials find use as pharmaceutical capsules, packaging, food service materials, and personal hygiene products. Although a high level of technical success was achieved, in Nov. 1993 the business was closed for financial reasons and the Novon technology was licensed throughout the world.

Assembled, managed and mentored a diverse group of 12 scientists and engineers who conceived and developed several new biodegradable compositions based on high molecular weight polysaccharides. Over a two year this group filed several valuable U.S. and foreign patent applications and the total intellectual property portfolio was subsequently sold for $45MM.

Performed technical evaluations and feasibility assessments of new and competitive materials to guide business managers and legal staff regarding acquisition of these technologies. Also functioned as technical liaison with attorneys and consultants from US. England, Sweden, and Japan, and functioned as the major scientific spokesperson representing the Novon at numerous national and international technical conferences, scientific meetings, and workshops.

1979 to 1991 — E. I. DuPont Co., Experimental Station, Wilmington, DE
Senior Research Scientist - Central Research and Polymer Products Departments

Conceived and developed novel bioresorbable compositions for medical applications and worked closely with joint-venture partners in the utilization of these materials for endovascular stents, implantable orthopedic fixation devices, drug delivery systems, and ultra-sound coronary imaging agents. This technology resulted in the formation of a successful joint-venture company known as Medisorb® which supplied medical grade materials to the device and pharmaceutical industries.

Developed methods for surface modification of polymeric biomaterials and evaluated these materials with respect to effects on cell growth, morphology and adhesion. Designed protocols to determine *in vitro* and *in vivo* resorption rates of bioresorbable polymers.

Discovered methods for the selective chemical and radiation crosslinking of blends of these polymers that resulted in the successful commercialization of a family of proprietary thermoplastic elastomers trade-named Alcryn® with sales exceeding $18MM annually over a 10 year period.

Education:

1977-1978, Post Doctoral (National Institutes of Health research fellow), L'École Normale Supérieure, Paris, France (laboratory of Prof. Marc Julia).

1975-1977, Post Doctoral (National Institutes of Health research fellow), Imperial College of Science and Technology, London, England (laboratory of Prof. Sir Derek H. R. Barton, Nobel Laureate).

1975, Ph.D. Organic Chemistry (minor in biochemistry), The Johns Hopkins University, Baltimore, Maryland.

1973, MA, Chemistry, The Johns Hopkins University, Baltimore, Maryland.

Academic Positions:

1994 - 1997	Adjunct professor, Royal Institute of Technology (Stockholm, Sweden): Developed and presented graduate level course in polymer science.
1988 - 1991	Instructor, American Chemical Society: Conceived, developed and presented short course entitled "Polymer Chemistry for Non-Chemists".
1987 - 1990	Instructor, Evening College, Widener University, Chester, PA: Developed and presented courses in polymer chemistry and biochemistry.

Professional Membership: American Chemical Society
Society for Biomaterials
San Diego BioCom

Issued U.S. Patents:

U.S, Pat. 6,797,311 (2004)	"Process for Impregnating a Porous Material with a Cross-linkable Composition"
U.S. Pat. 6,719,783 (2004)	"PTFE Vascular Graft and Method of Manufacture"
U.S. Pat. 6,660,827 (2003)	"Bioresorbable Hydrogel Compositions for Implantable Prostheses"
U.S. Pat. 6,534,560 (2003)	"Bioresorbable Compositions for Implantable Prostheses"
U.S. Pat. 6,521,284 (2003)	"Process for Impregnating a Porous Material with a Cross-linkable Composition"
U.S. Pat. 6,428,571 (2002)	"Self-sealing PTFE Vascular Graft and Manufacturing Methods"
U.S. Pat. 6,403,758 (2002)	"Bioresorbable Compositions for Implantable Prostheses (controlled release of pharmaceutical agents)"
U.S. Pat. 6,316,522 (2001)	"Bioresorbable Hydrogel Compositions for Implantable Prostheses"
U.S. Pat. 6,028,164 (2000)	"Bioresorbable Compositions for Implantable Prostheses"
U.S. Pat. 6,005,020 (1999)	"Bioresorbable Compositions for Implantable Prostheses"
U.S. Pat. 5,984,963 (1999)	"Endovascular Stents"
U.S. Pat. 5,854,382 (1998)	"Bioresorbable Compositions for Implantable Prostheses"
U.S. Pat. 5,852,114 (1998)	"Thermoplastic Polymer Blend Compositions with Accelerated Biodegradation"
U.S. Pat. 5,851,229 (1998)	"Bioresorbable Sealants for Porous Vascular Grafts"
U.S. Pat. 5,587,412 (1996)	"Esterified Starch Compositions"
U.S. Pat. 5,147,631 (1993)	"Micro-particles as Contrast Agents in Ultrasound Imaging"
U.S. Pat. 5,076,983 (1992)	"Biodegradable Poly(hydroxy acid) Films"
U.S. Pat. 4,918,696 (1991)	"Polylactide Compositions (controlled release of pharmaceutical agents)"

U.S. Pat. 4,902,515 (1990)	"Polylactide Compositions (micro-encapsulation of bioactive agents)"
U.S. Pat. 4,800,219 (1989)	"Polylactide Stereocomplex"
U.S. Pat. 4,766,182 (1988)	"Polylactide Compositions"
U.S. Pat. 4,719,246 (1988)	"Polylactide Compositions"
U.S. Pat. 4,613,533 (1986)	"Thermoplastic Elastomeric Compositions"
U.S. Pat. 4,555,528 (1985)	"Process for Foamed, Sulfur-Cured Polymer Blend Compositions"
U.S. Pat. 4,543,440 (1985)	"Curable Compositions of Elastomeric Carbon Monoxide Terpolymers"
U.S. Pat. 4,540,719 (1985)	"Process for Foamed, Sulfur-Cured Polymer Blend Compositions"

Additional U.S. applications pending